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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/785,215	02/20/2001	Martin Roland Jensen	3631-0107P	7660

2292 7590 08/14/2003

BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH, VA 22040-0747

EXAMINER
NICHOLS, CHRISTOPHER J

ART UNIT	PAPER NUMBER
1647	17

DATE MAILED: 08/14/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Offic Action Summary	Application No. 09/785,215	Applicant(s) JENSEN ET AL.	
	Examin r Christopher Nichols, Ph.D.	Art Unit 1647	

-- The MAILING DATE of this communication app ars on th cover sheet with the correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) *1,3,4,7-19,23-29,33 and 59-68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,7-19,23-29,33 and 59-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 February 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *14* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Application, Amendments, and/or Claims

1. The Amendment filed 23 June 2003 (Paper No. 16) has been received and entered in full. Claims 2, 5, 6, 20, 21, and 22 have been cancelled. Claims 1, 3, 4, 7-19, and 24-29 have been amended. Claim 68 has been added.

Withdrawn Objections And/Or Rejections

2. The objection to the Applicant's claim to priority as set forth at pp. 2-3 ¶4-5 in the previous Office Action (Paper No. 11, 19 December 2002) is *withdrawn* in view of Applicant's submission of a copy of Danish patent application PA 2000 00265 filed 21 February 2000. The Examiner stand corrected, as Patent Office records incorrectly show this as "Panama".

3. The objection to the declaration as set forth at pp. 3 ¶6 in the previous Office Action (Paper No. 11, 19 December 2002) is *withdrawn* in view of Applicant's submission of a substitute declaration (Paper No. 13, 23 June 2003).

4. The objection to the Specification as set forth at pp. 3 ¶7 in the previous Office Action (Paper No. 11, 19 December 2002) is *withdrawn* in view of Applicant's amendments (Paper No. 13, 23 June 2003).

5. The objection to the claims as set forth at pp. 3 ¶8 in the previous Office Action (Paper No. 11, 19 December 2002) is *withdrawn* in view of Applicant's amendments (Paper No. 13, 23 June 2003).

6. The Declaration under 37 CFR 1.132 filed 23 June 2003 (Paper No. 13) is sufficient to overcome the rejection of claims 1-29, 33, and 59-67 based upon 35 U.S.C. §112 ¶1 as set forth at pp. 3-14 ¶3-25 in the previous Office Action (Paper No. 11, 19 December 2002).

7. The rejection of claims 1, 11, and 22 under 35 U.S.C. §112 ¶2 as set forth at pp. 14-15 ¶26-28 in the previous Office Action (Paper No. 11, 19 December 2002) is *withdrawn* in view of Applicant's amendments (Paper No. 13, 23 June 2003).

New Objections And/Or Rejections

Oath/Declaration

8. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

> The oath or declaration is defective because:
> Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

Claim Objections

9. Claim **25** is objected to because of the following informalities: in claim 25, line 5, "of" should be "or". Appropriate correction is required.

Double Patenting

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

10. Claims **1, 3, 4, 7-19, 23-29, 33,** and **59-68 are** provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-22 and 27 of copending Application No. 10/204362. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims **1, 3, 4, 7-19, 23-29, 33,** and **59-68** are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *a method for reducing amyloid plaque burden in a mammal comprising effecting a presentation to said mammal's immune system of an immunogenically effective amount of said mammal's autologous Aβ or autologous*

APP wherein is introduced at least one isolated foreign T helper epitope by means of insertion, addition, deletion, or substitution, or by means of separate coupling to a polyhydroxypolymer carrier backbone of said foreign T helper epitope wherein said foreign T helper epitope is selected from a group consisting of Tetanus toxoid epitope, a diphtheria toxoid epitope, an influenza virus hemagluttinin epitope, and a P. falciparum CS epitope; and an Aβ or APP derived peptide sequence wherein said sequence is selected from the group consisting of amino acids 700-714 of SEQ ID NO: 2 and amino acids 672-714 of SEQ ID NO: 2, whereby immunization of said mammal with said analogue induces production of antibodies against the autologous Aβ or autologous APP in said mammal, does not reasonably provide enablement for *use of the method on all animals or use of other analogues or use of other T helper epitopes.* The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

12. The claims are drawn very broadly to methods of down-regulating autologous Ab and APP in any given animal via practicing the method of claim 1. The language of said claims encompasses both all animals, all Aβ analogues, and all T helper epitopes.

13. The specification teaches that Aβ variants with P2 or P3 inserted of Figure 1 can be used to practice the method of claim 1 where plaque burden is decreased or lessened. This would reasonably provide some relief from Aβ associated disorders such as Alzhimer's disease.

14. The specification fails to provide any guidance for treating non-mammalian animals, and since resolution of the various complications in regards to targeting the role a particular gene in an organism is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the

invention using the specification and the state of the art as outlined below, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of formulations with known Aβ and APP related homologues and analogues in a broad spectrum of animals. In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed. Additionally, a person skilled in the art would recognize that predicting the efficacy of using a specific polypeptide's role in non-mammals based solely on its function or disease-related roles in mammals as highly problematic (see MPEP 2164.02). Further, the Specification only teaches the use of the method in mice, an art-accepted representative of mammals. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

15. The following references are cited herein to illustrate the state of the art of amyloid plaques.

16. The unpredictability of using other non-specific and prophetically considered epitopes and sequences presents an undue burden of experimentation on the skilled artisan. It is not clear whether ALL animals have Aβ or APP. It is well established that humans, macaque monkeys, rats, mice, and polar bears all have Aβ and APP and are therefore liable to enjoy relief from Aβ

related disorders, no evidence is present to suggest that other animals, birds, reptiles, invertebrates, have Aβ or Aβ related disorders {see Selkoe *et al.* (20 February 1987) "Conservation of Brain Amyloid Proteins in Aged Mammals and Humans with Alzheimer's Disease." Science **235**(4791): 873-877 and Johnstone *et al.* (July 1991) "Conservation of the sequence of the Alzheimer's disease amyloid peptide in dog, polar bear and five other mammals by cross-species polymerase chain reaction analysis." Molecular Brain Research **10**(4): 299-305}.

17. On the nature of the invention, Eikelenboom *et al.* (2000) "Neuroinflammation and Alzheimer Disease: Clinical and Therapeutic Implications." Alzheimer Disease and Associated Disorders **14**(Suppl. 1): S54-S61 teaches that inflammatory responses to Aβ deposits are directly linked to the damage suffered from Alzheimer's disease (Figures 1 and 2; pp. S57). Thus the invention itself may inherently possess non-operative embodiments, and in the case of an Aβ based vaccine for use in humans, a lethal embodiment. While Eikelenboom *et al.* does note the success of Schenk *et al.*'s initial success in the mouse model, it was later found that the Aβ vaccine as practiced could be toxic to humans. Henceforth the scope of enablement rejection, where certain embodiments of the invention as claimed may provide relief, but not necessarily all, and still others may be toxic {see Elan: News 28 January 2002 "Elan and AHP provide an update on the phase 2A Clinical Trial of AN-1792."}.

18. Thus the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from mammalian animal model experiments to the practicing the method on all animals as exemplified in the references herein.

19. Claims **1, 2, 29, 60, 62,** and **63** are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Said claims contain material in parentheses therefore it is not clear as to what the Applicant's invention is and what weight to assign to the material in parentheses for terms of determining patentability. It is noted by the Examiner that the material are art-accepted abbreviations for well-known terms and are defined in the Specification and prior art thus further definition in the claims may be unnecessary.

20. Claim **12** is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

21. The term " substantially specific" in claim 12 is a relative term which renders the claim indefinite. The term " substantially specific" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear from the Specification or the prior art as to what the metes and bounds "substantially specific" are.

22. Claim **14** is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

23. The term "of lipid nature" in claim 14 is a relative term which renders the claim indefinite. The term "of lipid nature" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear from the Specification or the prior art as to what the metes and bounds "of lipid nature" are.

24. Claims **62** and **63** are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

25. The term "effective part" in claims 62 and 63 is a relative term which renders the claim indefinite. The term "effective part" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The metes and bounds of what constitutes or properties are necessary for an "effective part" of a cytokine or a heat shock protein are not clear.

26.

Summary

27. Claims **1, 3, 4, 7-19, 23-29, 33,** and **59-68** are hereby rejected.

28. The following articles, patents, and published patent applications were found by the Examiner during the art search and are here made of note:

a. US 2002/0077288 A1 (20 June 2002) Frangione *et al.*

b. US 2003/0068325 A1 (10 April 2003) Wang

c. US 6544518 B1 (8 April 2003) Friede *et al.*

d. Bishop and Robinson (November/December 2002) "The amyloid hypothesis: let sleeping dogmas lie?" Neurobiology of Aging **23**(6): 1101-1105

29. The following amendments are proposed by the Examiner to overcome the 35 U.S.C. §112 ¶1 rejection and thusly expedite prosecution of the instant application to allowance.

Proposed Amendments to Overcome 35 U.S.C. 112 Rejection

Claim 1 (Currently Amended) ~~A method for in vivo down-regulation of autologous beta amyloid (Aβ) protein or autologous amyloid precursor protein (APP) in an animal the method~~ A method for reducing amyloid plaque burden in a mammal comprising effecting a presentation to ~~the animal's~~ said mammal's immune system of an immunogenically effective amount of ~~at least one analogue of the animal's~~ said mammal's autologous Aβ or autologous APP wherein is introduced at least one isolated foreign T helper epitope ~~(T_H epitope)~~ by means of insertion, addition, deletion, or substitution, or by means of separate coupling to a polyhydroxypolymer carrier backbone of ~~T_H epitope~~ said foreign T helper epitope wherein said foreign T helper epitope is selected from a group consisting of Tetanus toxoid epitope, a diphtheria toxoid epitope, an influenza virus hemagluttinin epitope, and a *P. falciparum* CS epitope; and an Aβ or APP derived peptide sequence wherein said sequence is selected from the group consisting of amino acids 700-714 of SEQ ID NO: 2 and amino acids 672-714 of SEQ ID NO: 2, whereby immunization of ~~the animal~~ said mammal with ~~the~~ said analogue induces production of antibodies against the autologous Aβ or autologous APP in ~~the animal~~ said mammal.

Claim 9 (Currently Amended) The method according to claim 1, wherein the foreign T-cell epitope is immunodominant in ~~the animal~~ the mammal.

Claim 11 (Cancelled)

Claim 23 (Cancelled)

Claim 24 (Cancelled)

Claim 60 (Currently Amended) The method according to claim 1 ~~11~~, wherein the tetanus toxoid epitope is selected from the group consisting of ~~P2 (~~SEQ ID NO: 4~~)~~ and ~~P30 (~~SEQ ID NO: 6~~)~~.

Claim 61 (Currently Amended) The method according to claim 12, wherein the specific binding partner is selected from a group consisting of a hapten and a carbohydrate for which there is a receptor on the B-lympocyte or the APC.

Claim 62 (Currently Amended) The method according to claim 13, wherein the cytokine is selected from the group consisting of interferon-γ ~~(IFN-γ), an effective part of INF-γ~~, Flt3L, ~~an effective part of Flt3L,~~ interleukin 1 ~~(IL-1), an effective part of IL-1~~, interleukin 2 ~~(IL-2), an effective part of IL-2~~, interleukin 4 ~~(IL-4), an effective part of IL-4~~, interleukin 6 ~~(IL-6), an effective part of IL-6~~, interleukin 12 ~~(IL-12), an effective part of IL-13~~, interleukin 15 ~~(IL-15),~~ ~~an effective part of IL-15~~, and granulocyte-macrophage colony stimulating factor ~~(GM-CSF), an effective part of GM-CSF~~.

Claim 63 (Currently Amended) The method according to claim 13, wherein the heat shock protein is selected from the group consisting of HSP70, ~~an effective part of HSP70,~~ HSP90, ~~an effective part of HSP90,~~ HSC70, ~~an effective part of HSC70,~~ GRP94, ~~an effective part of GRP84,~~ and calreticulin ~~(CRT), and an effective part of CRT~~.

Claim 64 (Currently Amended) The method according to claim 14, wherein the third moiety ~~is of lipid nature and~~ is a lipid selected from the group consisting of a palmitoyl group, a myristyl group, a farnesyl group, a geranyl-geranyl group, a GPI-anchor, and an N-acyl diglyceride group.

Claim 68 (Currently Amended) The method according to claim 27, wherein the parenteral route is selected from the group consisting of the subcutaneous, the intracutaneous, and the intramusclular route.

Support for amendments at pp. 15 line 14-19; pp. 16 lines 10-11; pp. 21 lines 18-28

Gary L. Kunz

GARY KUNZ
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:00AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

CJN
August 11, 2003